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Award Number: DAMD17-03-1-0236

TITLE: Prostate Cancer Mortality and Herbicide Exposure in  
Vietnam Veterans

PRINCIPAL INVESTIGATOR: Steven D. Stellman, Ph.D.

CONTRACTING ORGANIZATION: Columbia University  
New York, NY 10032

REPORT DATE: April 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
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20041101 102

**REPORT DOCUMENTATION PAGE**Form Approved  
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

<b>1. AGENCY USE ONLY</b> (Leave blank)		<b>2. REPORT DATE</b> April 2004	<b>3. REPORT TYPE AND DATES COVERED</b> Annual (1 Apr 2003 - 31 Mar 2004)	
<b>4. TITLE AND SUBTITLE</b>  Prostate Cancer Mortality and Herbicide Exposure in Vietnam Veterans			<b>5. FUNDING NUMBERS</b>  DAMD17-03-1-0236	
<b>6. AUTHOR(S)</b>  Steven D. Stellman, Ph.D.			<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b> Columbia University New York, NY 10032  E-Mail: sds91@columbia.edu				
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			<b>10. SPONSORING / MONITORING AGENCY REPORT NUMBER</b>	
<b>11. SUPPLEMENTARY NOTES</b>				
<b>12a. DISTRIBUTION / AVAILABILITY STATEMENT</b> Approved for Public Release; Distribution Unlimited			<b>12b. DISTRIBUTION CODE</b>	
<b>13. ABSTRACT (Maximum 200 Words)</b>  <b>AIMS.</b> The association between exposure to military herbicides and subsequent death from prostate cancer will be investigated in a cohort of approx. 100,000 Vietnam veterans who applied to the Agent Orange Veteran Payment Program (AOVPP), which was administered by the US Federal District Court (New York) 1985-1994. Exposure opportunity will be assessed via a geographical information system (GIS) and herbicide and troop location databases previously developed by the investigators, with additional location data to be obtained from the National Archives. Cause of death will be ascertained via National Death Index (NDI) searches. Epidemiological analyses will include comparison of age-specific prostate cancer death rates, proportional mortality ratios (PMR), standardized mortality ratios (SMR), and proportional hazards methods, using unexposed veteran as a reference population. <b>RESULTS.</b> Systems were developed to locate and abstract military unit histories, and two NDI submissions were carried out. By December, 1999, 25,132 claimants had died. The first of two NDI searches yielded 112 prostate cancer deaths; a second is planned early in Year 2. Microfilm record abstraction of military unit histories is continuing and a nested case-control study is in progress.				
<b>14. SUBJECT TERMS</b>  Prostate cancer, Vietnam veterans, Agent Orange, herbicides, dioxin			<b>15. NUMBER OF PAGES</b> 19	
			<b>16. PRICE CODE</b>	
<b>17. SECURITY CLASSIFICATION OF REPORT</b> Unclassified	<b>18. SECURITY CLASSIFICATION OF THIS PAGE</b> Unclassified	<b>19. SECURITY CLASSIFICATION OF ABSTRACT</b> Unclassified	<b>20. LIMITATION OF ABSTRACT</b> Unlimited	

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)  
Prescribed by ANSI Std. Z39-18  
298-102

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## INTRODUCTION

Prostate cancer is the most common cancer diagnosed among males in the US and other Western countries<sup>1</sup>, yet little is known about its causes. Elevated prostate cancer risks have been associated with occupational exposure to phenoxy herbicides and other agricultural chemicals<sup>2,3</sup>. One large group of men who may be at increased risk from exposure to phenoxy herbicides consists of veterans of the Vietnam War (1962-1975), during which the US military sprayed over 19 million gallons of phenoxy and other herbicides in the Republic of Vietnam (RVN). Many of the 3.2 million servicemen stationed in RVN were assigned to military duties which involved exposure to these herbicides and to 2,3,7,8-tetrachloro-*p*-dibenzodioxin (TCDD or dioxin), a carcinogenic contaminant of Agent Orange.<sup>4</sup> An expert Committee of the Institute of Medicine (IOM) concluded that there is "limited/suggestive evidence" of association with prostate cancer.<sup>5,6,7,8</sup> but this conclusion is based on studies of non-veteran populations, or on very small veteran studies.<sup>9</sup> The purpose of this study is to evaluate the association between exposure to military herbicides and subsequent prostate cancer mortality in a cohort of about 100,000 claimants to the Agent Orange Veteran Payment Program (AOVPP). The AOVPP was created by the Eastern US Federal District Court (New York) to administer the settlement of a class-action lawsuit of veterans against chemical manufacturers. Fact and cause of death among the 26,000 expected deaths in this cohort are being ascertained via Social Security and National Death Index searches. Exposure is being assessed from military records abstracted from the extensive AOVPP microfilm files, using our geographic information system (GIS) database of military unit locations throughout the War, and an exposure assessment methodology that we developed under a contract from the National Academy of Sciences.<sup>10,11</sup> Measures of association include comparisons of age-specific rates with unexposed veterans and the general population, and comparison of proportional mortality ratios, standardized mortality ratios, and odds ratios generated from proportional hazards models among subgroups with different estimated levels of exposure opportunity.

## BODY

The Year 1 tasks outlined in the approved Statement of Work (SOW) are shown in Table 1, below.

**Table 1. Approved SOW tasks for this funding period (01 April 03 to 31 March 04)  
Year 1**

<i>Task 1.</i> To obtain the causes of death for 16,000 known decedents (Months 1-6).	
<i>Task 1a.</i> Months 1-2	Initiate application process for National Death Index and Social Security vital status searches.
<i>Task 1b.</i> Months 3-8	Obtain cause-of-death file for 16,000 known decedents from National Death Index NDI-Plus and incorporate into AOVPP database; resolve conflicts.
<i>Task 1c.</i> Months 3-12 <sup>a</sup>	Obtain from Social Security Administration vital status for 70,000 applicants who were alive at time of filing claims.
<i>Task 1d.</i> Months 13-18	Obtain cause-of-death data from NDI-Plus for approximately 10,000 applicants reported deceased by SSA
<i>Task 2.</i> To obtain Agent Orange Exposure Opportunity Scores for AOVPP cohort members	
<i>Task 2a.</i> Months 2-12 <sup>b</sup>	Code military unit with UIC code based upon information in microfilm copy of military records.
<i>Task 2b.</i> Months 2-12 <sup>b</sup>	Refer to primary reference matter for supplementary military history data.
<i>Task 2c.</i> Months 3-12 <sup>c</sup>	Use GIS to obtain Exposure Opportunity Scores from UICs.

<sup>a</sup> This task continues into Year 2, months 13-18.

<sup>b</sup> This task continues into Year 2, months 13-20.

<sup>c</sup> This task continues into Year 2, months 13-21.

**Introduction.** The purpose of this project is to determine whether there is an association between an exposure (military herbicides in Vietnam) and an outcome (prostate cancer mortality). Task 1 deals with obtaining cause of death outcomes that will be the numerators for the PMR and SMR studies. This task, which also covers identification of cases and potential controls for the nested case-control study, will be completed early in Year 2. Task 2 deals with determining exposures and depends in part on completion of Task 1 (identifying cases and controls for the nested case-control study). It will extend into Year 2 as originally planned.

When the study began, none of the outcomes was known besides fact of death. Therefore, data for military unit history assignments (the critical first step in exposure assessment) was gathered by systematically extracting microfilm data for decedents according to their microfilm sequence, with different microfilm operator teams starting from different places in the microfilm archives to reduce potential filing-date bias. The first NDI search identified 112 veterans whose underlying cause of death was prostate cancer, and 11 more with prostate cancer mentioned but with a different underlying cause. Up to five

controls matched on birth year ( $\pm 2$  yrs) and state were then selected for each case (542 controls for the 112 cases). The military records searches subsequently focused on this nested case-control sub-population. The databases for these searches will be expanded to include the results of the forthcoming death search in Year 2.

We also concluded that we would make the most efficient use of resources by completing the coding of the military units for the case-control study with all available microfilm data (Task 2a) prior to going to the National Archives to fill in gaps in our location databases (Task 2b) and computing exposure scores (Task 2c), so the latter sub-tasks are being deferred to Year 2. As noted below, both can be completed well within the grant period and deferring them will not affect the overall timetable. Task 3, dealing with analysis, is scheduled for Year 2.

**Task 1. To obtain the causes of death for 16,000 known decedents**

**Task 1a - Initiate application process for National Death Index and Social Security vital status searches.** The requisite application was submitted to the National Death Index on June 26, 2003. Although the NDI application form was essentially complete by April 29, 2003, formal submission had to await official receipt of the Columbia University IRB approval as well as that of the U.S. Army Medical Research and Materiel Command Office of Regulatory Compliance & Quality, which requested a series of clarifications before finally releasing the project.

**Task 1b - Obtain cause-of-death file for 16,000 known decedents from National Death Index NDI-Plus and incorporate into AOVPP database; resolve conflicts.** This task consists of several sub-tasks:

Task 1.b.1. Construct a definition of the cohort

Task 1.b.2. From the master AOVPP database create a file of known decedents who satisfy the cohort definition. The file must contain the data elements required by NDI-Plus and must conform to NDI-Plus format specifications.

Task 1.b.3. Submit the data file to NDI-Plus.

Task 1.b.4. Receive results from NDI-Plus.

Task 1.b.5. Develop and implement a quality assurance plan for accepting records returned by NDI-Plus and apply that plan to the records received from NDI.

**Task 1.b.1. Construct a definition of the cohort.** Definitional note: The AOVPP was open to both living and deceased veterans. Claims for deceased veterans had to be filed by a surviving family member. The AOVPP contains a field "claim\_type" which is either 'D' for disability claims, or 'S' for survivor claims. The terms "survivor claims," "survivor claimants," and "survivor applicants" thus refer to deceased veterans. The AOVPP master file contains 20,653 survivor claims and 85,110 disability claims. Not all claimants are eligible for this study. An individual of either sex is a member of this cohort who meets all these conditions:

1. Was a claimant to the Agent Orange Veteran Payment Program (AOVPP), or was a deceased veteran on whose behalf a claim was filed by a survivor.

2. *Was an Active Duty member of the United States Armed Forces (Army, Navy, Marines, Air Force, Coast Guard) during the "official" Vietnam War period: February 28, 1961, through May 7, 1975.* This condition must be verified by inspection of the claimant's military records (DA-20, DD-214, etc.) which must show service during official War years.
3. *Was discharged alive from the Armed Services.* Individuals killed in action or who otherwise died during active duty were not eligible for compensation and thus cannot be a member of the cohort.
4. *Was alive on January 1, 1979, the earliest date for National Death Index records.* We excluded 2,997 individuals who died before January 1, 1979. This exclusion allows a reasonable latency period and avoids the effort and expense of nosologically coding nearly 3,000 death certificates directly from microfilm. The latency for most of the excluded individuals is very short, so that cancer deaths are unlikely to be related to wartime exposures. However, there is a potential for bias if they were exposed to a fast-acting carcinogen. If an association with prostate cancer is found in future analyses, we will seek funding to code these death certificates.
5. *If deceased prior to January 1, 1995, the cause of death must not be from homicide, suicide, or accident (ICD-9 E-codes).* This exclusion is to maximize the likelihood that all members of the cohort have comparable exposure data. A Court-mandated condition of eligibility was that death not have been due to homicide, suicide, or accident, and no effort was made to obtain records from these claimants. It is assumed that all claimants who survived past the closure of the fund (December 31, 1994) had equal opportunity to submit valid exposure information. Since they are also at risk to die from any cause of death, there is no reason to restrict causes beyond this date.

***Task 1.b.2. From the master AOVPP database create a file of known decedents who satisfy the cohort definition. The file must contain the data elements required by NDI-Plus and must conform to NDI-Plus format specifications.***

A file of 16,047 records that met all of the above conditions was extracted from the master AOVPP database and formatted according to specifications in the NDI User's Manual.<sup>12</sup> The file contained the following fields for each veteran: Last Name, First Name, Middle Initial, Social Security Number, Date of birth, Sex.

***Task 1.b.3. Submit the data file to NDI-Plus.***

The file of 16,047 known decedents was submitted to the National Death Index on 29 August, 2003.

**Task 1.b.4. Receive results from NDI-Plus.**

On September 19, 2003, the National Death Index returned to us a CD containing the search results, as a set of 10 separate files shown in Table 2.

**Table 2. National Death Index NDI-Plus output**

No.	Name	Records	Contents
1	SUMMARY	3 pp	Overall summary
2	REPORT	5,972 pp	List of NDI records that meet minimum matching criteria
3	COMPRESS	1,982 pp	Same as File 2 – compressed
4	REQFORMS	Not used	Meant for requesting death certificates from states
5	COMBINED	71,089 records	User data and NDI match criteria in a single line
6	MATCH	15,962 records	User records that generated at least 1 NDI match
7	NOMATCH	83 records	User records that generated no NDI match
8	REJECTS	0	User records that failed format standard
9	CAUSE	16,097 records	User record + NDI "match" + causes for that match Each user record may have more than one match
10	PRTCAUSE	2,839 pp	Printable version of File 9

Four of these files are of primary importance.

- The MATCH file indicates that NDI was able to find at least one match for 15,962 of the 16,047 records that we submitted.
- The NOMATCH file indicates that NDI was unable to find any matches for 83 records. From a sample of the death certificates in the microfilm archives we determined that the great majority of these deaths occurred outside the United States (e.g., Canada, UK, many other countries). We plan to print copies of the death certificates and have them coded by a trained nosologist.
- The COMBINED file contains as many records as NDI found matches for user records. The file contains 71,089 records, indicating that NDI found an average of 4.5 matches for each record we submitted. The number of matches per user record ranged from 1 to 50 (the maximum NDI will report for any user record). Each record in the Combined file pertains to a single match for a given user record, and contains (a) the data originally supplied by the user; (b) an encoded version of the matching fields that indicates the quality of the match (e.g., which digits of the SSN matched, whether first name matched, etc.); and (c) a probabilistic matching score based upon a weighting system that takes into account rarity of names, initials, and birthdates in the general population.
- The CAUSE file contains cause of death data for those matching records that NDI deems sufficiently likely to be "true" matches.

No. AOVPP records submitted = 16,047

No. "lost" by NDI<sup>a</sup> = - 2

No. processed by NDI = 16,045

No matches found = - 83

At least 1 match found = 15,962

<sup>a</sup> These records were subsequently resubmitted and processed by NDI

The distribution of records that were returned to us from NDI by multiplicity of SSN's is shown in Table 3.



**Table 3. Records returned to us by NDI by SSN multiplicity**

No. records returned =		16,097	records
No. unique SSNs =		15,962	records
Difference =		135	records
No. SSNs appearing 1x =	15,832	→	15,832 records
No. SSNs appearing 2x =	125	→	250 records
No. SSNs appearing 3x =	5	→	15 records
TOTAL	15,962	→	16,097 records

A preliminary tabulation was made of the distribution of causes of death. The five leading causes are shown in **Table 4**:

**Table 4. Leading causes of death among survivor claims**

Lung cancer	2,766
Cardiovascular diseases	2,238
Lymphoma	610
Colon cancer	564
Chronic liver disease/cirrhosis	535

The number of records listing prostate cancer as the underlying cause was 112. Eleven additional DC's listed prostate cancer but not as underlying cause. These initial numbers are small, but it is to be remembered that they are based on claims filed through 1994, in a cohort with median birth year 1946, and include deaths dating back to 1979. The next round of death searches will cover deaths that occurred between 1994 through 1999, in a cohort that is continuing to age, and is expected to yield proportionally more prostate cancers. An unexpectedly large number of deaths (n = 633) were coded to "Malignant neoplasm – NOS" (ICD-9 = 199). In Year 2 we will examine a sample of any Attending Physicians' Statements or other microfilmed medical records to determine whether information about a terminal illness or cause of death is available.

***Task 1.b.5. Develop and implement a quality assurance plan for accepting records returned by NDI-Plus and apply that plan to the records received from NDI.***

Quality assurance is essential to this project, but is time-consuming and labor-intensive. To explain why, it is necessary to understand what NDI does and does not provide. The National Death Index is not a follow-up agency. It provides neither fact of death nor death certificates for any individual *de novo*. Its function is to confirm that a death certificate exists somewhere in the United States for an individual for whom the investigator already possesses information. The user submits a list of individuals along with critical data fields, and NDI confirms, if it can, that a death certificate exists for each person, based upon application of a matching algorithm that takes into account the SSN, name, and other user-supplied data. The matching algorithm casts a very wide net, and often yields "matches" based on only a few digits of the SSN and/or liberal misspellings of names. Consequently, the results file called "Combined" can contain many potential matches for each submitted record. It is the user's responsibility to decide which potential matches are true matches and which are not. We therefore made a systematic examination of the NDI results with the goal of making a set of decision rules for accepting or rejecting the NDI cause of death records.

**Death Certificate Validation Studies.** A valid death certificate was an AOVPP requirement for eligibility as a survivor claimant, and all death certificates received were microfilmed and indexed. It was therefore possible to validate the records offered by NDI as matches for our records by visual comparison of the microfilmed death certificate with cause-of-death data received from NDI. Two validation studies were done, one for NDI records described as "exact" matches and one for all other NDI records. Both the "CAUSE" and "COMBINED" files returned by NDI contain a field which displays an \* to show that a given record exactly matches the user's record (in our submission, this applies to all of the following fields: SSN, first name, middle name, last name, sex, and date of birth). Table 5 shows the breakdown of exact and non-exact matches.

**Table 5. Distribution of "exact" and non-exact matches in records returned by NDI**

No. of exact matches	13,399	(83%)
No. of non-exact matches	<u>2,698</u>	(17%)
TOTAL	16,097	

**Validation Study 1: Verification of "exact" matches.** The goal was to verify that NDI had correctly identified death records for our study subjects by visually comparing a sample of microfilmed death certificates with both the user file that we submitted to NDI and the cause of death result file that we received from NDI.

**Method:** We set an initial goal of approximately 100 death certificates. Our strategy was first to identify any discrepancies between the microfilm copies of these certificates and the NDI search results. We would examine additional death certificates only if major discrepancies arose in this initial set. Claims documents, including death certificates, occur randomly within the microfilm archives, and the more than 16,000 death certificates in the archives are fairly evenly distributed among 861 reels, with an average of 18.6 death certificates per reel. (There are 18 boxes with 48 cartridges each). To minimize time as well as wear and tear on the microfilm, we assumed that it would be acceptable to confine our inspection to a single box of 48 consecutively numbered reels. We chose box 5, which contains reels 183 through 230, as representative of all boxes. We selected every seventh reel in box 5 and made a list of the frame numbers of all of the death certificates on each reel (Table 6 below).

**Table 6. No. of death certificates for NDI "exact" matches, by microfilm cartridge**

Cartridge	N DC's
183	18
200	15
207	18
214	14
221	14
228	22
TOTAL	101

A Microsoft Access query linked each death record to the cause of death data in the NDI Combined file and also linked each ICD-9 cause of death code to its narrative text description. The Microsoft Access report generator then produced a printed listing of all entries in the cause of death section, arranged visually in frame order. Using a separate

Access-driven query, a microfilm operator then located each of the 101 death certificate images on the appropriate cartridge using a Minolta MS-6000 microfilm transport/scanner, and created a pdf image using Adobe Acrobat, for visual comparison with the cause of death listing from the NDI file.

**Results.** All but one of the 101 images listed in the master index to the AOVPP archives were located and scanned. One document could not be physically located at or near the indicated frame number. The 101 documents, including the one not found, represented 98 claimants. One pair of microfilm images was actually two halves of a torn death certificate; a second pair of documents contained a death certificate and a confirmatory autopsy report; a third pair of death certificates were for a father and his child, and only the father's death certificate was relevant to the NDI search. By visual inspection, all of the death certificates belonged to the correct veterans; that is, the information on the death certificate matched data in the AOVPP master data table, including dates of birth and death, sex, name, and SSN. For 79 of the 98 deceased claimants (81%), the state of death of death certificate filing matched the state from which the claim itself was filed. There was no claim filing address listed in the AOVPP file for six certificates. For the remaining 13 claims, the state of filing was different from the state of death, although many were neighboring (e.g., MD/WV, NJ/PA, AL/MS). There is no reason to expect perfect concordance on this item, since surviving kin need not have lived in the same state as the veteran.

We compared the cause of death sequence on death certificates with the entity-axis sequence provided by NDI. The concordance was exact in all but ten cases that lacked information for the following reasons:

No. death certificates	Reason for lack of validation
4	Microfilm image too faint to read
4	DC issued by county without cause section
1	Cause "pending" on DC submitted to AOVPP
1	New York City – NDI not yet authorized to furnish cause [NYC has not yet released cause of death information]

**Conclusion.** In every instance in which validation could be reasonably attempted, the NDI record was found to match the physical death certificate. We conclude that we can accept the cause-of-death data from NDI records that are flagged with a \* in col. 165 as correctly pertaining to the AOVPP claimant to whose record they are attached.

**Validation Study 2: Verification of "non-exact" matches.** The "Cause" file contained 2,698 records without an \* to indicate an exact match. As with the exact matches, we assumed the Box 5 contains a representative sample of all death certificates. We scanned every such death certificate in that Box, and compared the image of each death certificate with a printout of the corresponding record in the CAUSE file. Box 5 contains reels 183 through 230. There were 166 non-exact match death certificates in box 5. Table 7 shows the number of non-exact match death certificates by cartridge number.

**Table 7. Number of non-exact match death certificates in Box 5,  
by cartridge number**

Cart. No.	No. Death Certs.	193	1	208	4	221	5
183	6	195	4	209	6	223	1
184	3	197	8	210	3	224	3
186	6	198	4	212	2	225	8
187	4	199	11	213	2	226	2
188	5	200	5	214	3	227	1
189	1	201	11	215	4	228	3
190	6	202	7	216	1	229	3
191	1	203	9	217	2	230	4
192	1	205	4	218	1		
		206	3	219	5		
		207	1	220	2		

Microfilm clerks located and visually compared each of the 166 non-matching death certificates with the cause of death data that had been returned to us by NDI. In every case it was the same person as in the NDI record.

There were no instances in which the DC and NDI differed as to cause of death. However, there were 2 death certificates for which the cause could not be verified. One DC showed ethanolism and COPD, and had the phrase "pending further study." The NDI entity axis shows a motor vehicle accident. We believe that the DC was subsequently updated. The second DC contained only the administrative portion, omitting the cause of death section. We conclude that all NDI records with status = 1 may be accepted as belonging to the correct AOVPP claimant.

***Task 1c. Obtain from Social Security Administration vital status for 70,000 applicants who were alive at time of filing claims.***

When IRB approval was received, a death record search was made using a list of SSN's of all AOVPP claimants after removing the 20,653 known decedents. In other words, this list included all veterans not known to have died at the time they filed their claims with the AOVPP. This search yielded a file with 14,683 potential decedents, including name, date of birth, and date of death as they appear on the death certificate. This file was subjected to a number of quality assurance tests, including comparison of the last name with data in the AOVPP files. A total of 576 death records failed to match the AOVPP data on last name. Most of the mismatches were due to trivial misspellings (e.g., Hargraves in one file, Hargreaves in the other), or occurred among Puerto Ricans with hyphenated last names (e.g., Lugo in one file, Lugo-Santiago in the other). A total of 71 records were clearly mismatched, and were due 1-digit mismatches in SSN, as determined by manual searching. These 71 deaths were obviously not for AOVPP claimants; manual searches for the 71 intended cohort members using the name rather than the SSN revealed that seven had in fact died, and that the AOVPP file and the death certificate disagreed by 1 digit in the SSN. *No further effort will be made to resolve these discrepancies because the NDI searches are highly robust to such typographical errors, and will yield the correct decedent even with an SSN that is 1 digit off.*

On February 2, 2004, we conducted a second death search using all remaining veteran SSNs. An additional 1,366 death records were obtained. After additional quality assurance tests, the two files of deceased claimants were combined. Records for all 9,805 persons who died through December 31, 1999, were formatted for a National Death Index search. [NDI submission occurred on April 9, 2004, which is in grant Year 2.]

***Task 2 To obtain Agent Orange Exposure Opportunity Scores for AOVPP cohort members***

**Task 2a. Months 2-12<sup>b</sup> Code military unit with UIC code based upon information in microfilm copy of military records.**

<sup>b</sup> This task continues into Year 2, months 13-20.

This sub-task includes the most labor-intensive activities of the study. A computerized index exists which permits rapid location of individual documents by cartridge and frame. Assembling all relevant documents for a given veteran is not trivial because documents in the microfilm archives are organized roughly in chronological order by date of filing and not by veteran. One veteran's documents may be scattered over many different microfilm cartridges. For example, veteran 111223333 may have one document on cartridge 030, two documents on cartridge 377, and one document on cartridge 652. In order to minimize wear and tear on the fragile microfilm reels (some of which are nearly 20 years old), and to maximize scanning efficiency, it was decided to locate and scan records sequentially by cartridge, and in the frame order in which the records appear on the cartridge.

This decision was implemented by naming a Data Coordinator, Ms. Carrie Tomasallo, whose job is to create and manage a set of databases which contain the ID numbers and locations of all microfilm and other documents required for the study. The databases belong to an integrated system of Microsoft Access Tables, Queries, and Forms. The Data Coordinator also creates and maintains a complete set of archival DVD's so that all document folders and their contents easily be retrieved and reconstructed in case of disaster occurring to any individual computer in this project. This effort was substantially streamlined through collaboration with a programming specialist who aided in designing the systems for file management and for secure high-speed transfer of data between microfilm operators, the data coordinator, and the military records specialist.

**Task 2.a.1. Using the AOVPP microfilm index, the locations of all desired military records (e.g., for nested case-control subjects) are identified by cartridge and frame, a database containing their locations is created, and the microfilm images are scanned to electronic image files.**

A sample Form ("Form A") used by the microfilm operators is shown in Figure 1. The form indicates the cartridge, frame, and document type for the next document to be located. The Minolta MS-6000 transport is equipped with a Mars 2 controller keypad into which the operator keys the frame number (0007 in the example). The transport advances

to the desired frame. The operator confirms visually that the document pertains to the veteran whose name and SSN also appear in the form. He or she then scans the document using the Adobe Acrobat import feature (the MS-6000 is recognized as a TWAIN scanning device) and saves it as a pdf file, under a file name that is a composite of the SSN, cartridge, frame, and document type. This naming convention facilitates subsequent file management functions, such as sorting and re-organizing document folders. In the example shown, the Exposure Information Form (a 4-page document) would be saved under the name 252629655\_087\_0007\_04.pdf. To minimize microfilm wear, documents in Form A appear in frame order so that the microfilm is always advancing.

**Figure 1. Screen shot of document locator "Form A" used by microfilm clerk to locate and scan military records (dummy record shown)**

The microfilm operators are trained to recognize and scan many different types of military documents, listed in Table 8.

**Table 8. Documents to be scanned by microfilm operators**

Branch of Service and Form type	Type of Form	Information Available
<b>ARMY</b>		
DA Form 20/24/66/2-1	Personnel Qualification Records	Dates and location of foreign service; units of assignment with "in" and "out" dates; MOS (duty code); description of primary duty; awards and medals
Special Orders		Dates of transfer from unit to unit; dates of awards, medals, promotions, etc. and unit assignment at the time
<b>MARINES</b>		
NAVMC 118(3)	Record of Service	Units of assignment with "in" and "out" dates; primary duties
NAVMC 118(9)	Combat History/Expeditions	Dates "in" and "out" of Vietnam operations; awards with dates and units of assignment at the time
NAVMC 118(17)	Sea and Air Travel Embarkation Slips	Dates of transfer to and from Vietnam
Unit Diaries		Listings of veterans assigned to the specific units for specific dates; unit movements
<b>AIR FORCE</b>		
AF FORM 7/11	Airman and Officer Military Records	Dates and locations of foreign service; units of assignment with "in" and "out" dates; Air Force Base assignments, duty

		codes, awards and medals
Performance Reports		Unit of assignment with "in" "out" dates; Air Force Base of assignment, description of duties
<b>NAVY</b>		
NAVPERS 601(12)	Transfers and receipts	Dates of transfer between units and ships
NAVPERS 601(13)	Administrative remarks	Units and/or ships of assignments, dates, some ship activities
<b>ALL BRANCHES</b>		
DD214, DD215	Report of Transfer or Discharge	Dates of service; dates of foreign service; last unit of service and awards
Unit Histories (Army, AF, Marines)		Unit activities and movements
Ships' Histories (Navy, Marines)		Ship activities and movements

If the operator determines that the document should not be scanned (e.g., if it is not one of the types listed in Table 8 or does not belong to the veteran in question), the "Reason not scanned" field is completed. The operator must click on the "Next Record" button to release the record. This sets a flag which the Data Coordinator uses to determine which documents have been scanned.

#### **Microfilm scanning results**

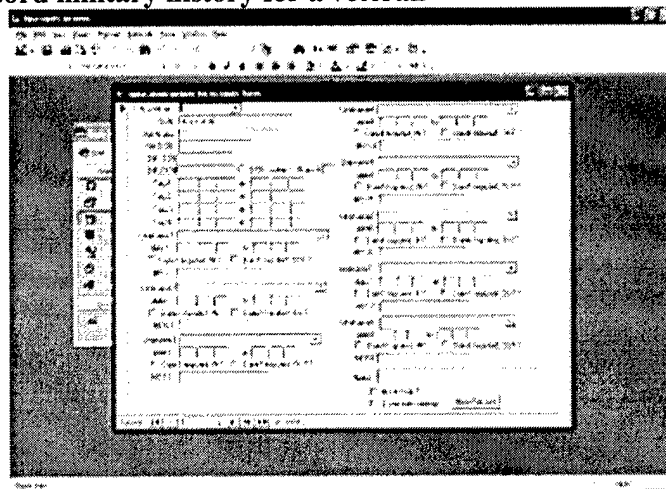
At the end of Year 1, military document microfilm images for 6,508 veterans had been scanned. Of these, image folders for 4,314 veterans were transmitted to the Military Records Specialist for unit assignment coding, along with paper records for 773 additional veterans for a total of 5,807 veterans (the paper files had been in dead storage since the closing of the AOVPP offices in 1994; they are also in the microfilm archive, but use of paper records resulted in cost savings for the project).

#### **Task 2.a.2. The military records specialist reads and interprets the scanned documents created in Task 2.a.1., constructs the veteran's military unit assignment history, and enters it into a database**

All document image files created by the microfilm operators are maintained in a "holding" folder by the Data Coordinator. The Data Coordinator periodically re-organizes this folder by identifying those veterans whose document set is complete (i.e., all documents in the microfilm index have been scanned). The re-organization places the complete set of document images for each veteran into a folder whose name is the same as the veteran's SSN. The folders for completed veterans are transmitted to the Military Records Specialist, Ms. Francine Benjamin, whose job is to read all of the records for each veteran, and construct his or her military unit history. This history is a chronological listing of the military units to which the veteran belonged during his/her tour of duty in Vietnam. The history is entered directly into a form ("Form B"), shown in Figure 2. Form B contains space to record up to 18 military unit assignments plus an unlimited number of military occupation specialties (MOS). Use of the Form B is driven by a query which operates only on records not yet completed. Form B permits the Military Records Specialist to impute some unit assignment dates based on a strict set of imputation rules; the database distinguishes imputed from officially documented dates. Periodically, the

Data Coordinator updates her master file of military unit assignments using fresh unit assignments from the Military Records Specialist.

**Figure 2. Screen shot of "Form B," used by Military Records Specialist to record military history for a veteran**



#### **Unit History Assignment Results**

*Cohort Study.* By the end of Year 1, the Military Records Specialist had reviewed data for 5,087 veterans, of which sufficient data existed to code 3,343 (66%) completely. An additional 616 veterans (12%) had data to code only part of their Vietnam tours of duty, while 993 (20%) had no usable data. A small number (135 or 3%) were found to be ineligible based on information in their military files and had to be excluded from the study.

*Nested case-control study.* Record review was complete for 97 of the 654 veterans in the case-control study with prostate cancer as underlying cause ( $654 = 112 \text{ cases} + 542 \text{ controls}$ ). Of these initial 97 veterans, 70 had complete military histories, 11 could only be partially coded, and 16 had no military record data.

*Tasks deferred to Year 2.* As noted in the Introduction, the two following sub-tasks, which were originally scheduled in both grant years, have been deferred entirely to Year 2 as an efficiency measure. This delay will have no noticeable effect on the timetable for completion of the Project.

#### **Task 2b. Refer to primary reference matter for supplementary military history data.**

For those military units for which location tracking data are missing or incomplete, the Vietnam collection at the National Archives and Records Administration (NARA) will be consulted. To maximize efficiency and minimize costs, this task will be deferred until the majority of existing microfilm records have been scanned and inspected, at which time the Co-PI (Jeanne M. Stellman, PhD) and military consultant (Lt. Col. Richard Christian, Jr., USAR – Ret.) will re-visit NARA and seek to fill in the missing



information from Theater records. We anticipate that this task will be carried out in months 15-18.

***Task 2c. Use GIS to obtain Exposure Opportunity Scores from UICs.***

For each veteran, the Unit Identification Code (UIC) is used to construct a location history record for each study subject. This history is the input to the GIS software Herbicide Exposure Assessment – Vietnam (HEA-V). Execution of the software is essentially instantaneous, so that it can be run at any time location history data are available. This task will be deferred until the location histories have been constructed for all of the subjects in the nested case-control study. We anticipate that this task will be carried out in months 15-18.

**SUMMARY OF YEAR 1 ACTIVITIES**

The main activities of Year 1 have involved preparation, testing, and implementation of the extensive computer databases and programs previously described, vital status update for the entire AOVPP cohort through December 31, 1999, and the first of two planned rounds of National Death Index submissions and several studies to validate NDI data. The second NDI submission will take place early in Year 2, after which work will focus on the nested case-control study.

**KEY YEAR 1 RESEARCH ACCOMPLISHMENTS**

- **Characterized AOVPP veteran population and constructed a cohort definition**
- **Constructed databases and forms for document retrieval and unit assignment coding**
- **Submitted file of survivor claimants (n = 16,047) to National Death Index, yielding 13,399 exact matches (including some duplicates to be resolved), 2,698 non-exact matches, and 83 non-matches; carried out quality assurance, including two validation studies for exact and non-exact matches, respectively**
- **Microfilm military documents for 6,508 veterans were scanned by operators**
- **Documents for 5,087 veterans were reviewed by the Military Records Specialist**
  - 3,343 (65.7%) could be completely coded for unit histories
  - 616 (12.1%) could be partially coded for unit histories
  - 993 (19.5%) had no usable data
  - 135 (2.7%) were determined to be ineligible based on information in the military records
- **Identified 112 prostate cancer cases among survivor claimants and 542 matching controls selected and scanning of military records begun**
- **Vital status follow-up identified 9,805 eligible cohort members who died after filing their AOVPP claim, through December 31, 1999, in preparation for second National Death Index search in Year 2**

## **REPORTABLE OUTCOMES**

There are no scientifically reportable outcomes in Year 1, whose activities have all been directed at establishing data systems, acquiring data, and implementing quality assurance procedures. Based on data received in Year 1 and anticipated results of the second National Death Index search, which was submitted just at the end of Year 1, data analyses for proportional and standardized mortality will proceed on schedule early in Year 2.

## **CONCLUSIONS**

Work on this funded project is proceeding on schedule and without any serious delays. Most importantly, a highly integrated set of manual and computer procedures for acquiring electronic images of military records from the vast microfilm archives (over 1 million documents spread over nearly 900 reels) has been implemented efficiently with suitable quality assurance procedures, resulting in a smooth flow of data between the microfilm operators and the military records specialist. Vital status updates and subsequent National Death Index searches have also gone smoothly, and have resulted in confirmation of over 25,000 deaths with full ICD-9 cause detail.

This is a unique and valuable cohort, and is the largest cohort of Vietnam veterans assembled for an epidemiological study for which extensive environmental exposure data are available. Nearly all prior studies have relied upon surrogate exposure measures, some of which lack even simple measures of face validity. Our expectation is that the data analyses planned for Year 2 will be of considerable value to the Institute of Medicine Committee which biennially reviews studies of Agent Orange and Vietnam Veterans, and which to date has classified the evidence for a link with prostate cancer as only "limited/suggestive."<sup>8</sup>

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## REFERENCES

- <sup>1</sup> Hsing AW, Tsao L, Devesa SS. International trends in prostate cancer incidence and mortality. *Int J Cancer* 2000; 85:60-67.
- <sup>2</sup> Blair A, Zahm SH. Cancer among farmers. *Occup Med* 1991; 6:335-354.
- <sup>3</sup> van der Gulden JWJ, Kolk JJ, Verbeek ALM. Prostate cancer and work environment. *Am J Occup Med* 1992; 34:402-409.
- <sup>4</sup> Stellman JM, Stellman SD, Christian R, Weber T, Tomasallo C. The extent and patterns of usage of Agent Orange and other herbicides in Vietnam. *Nature* 2003;422:681-7.
- <sup>5</sup> Institute of Medicine 1994. Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*. Washington, DC: National Academy of Sciences Press.
- <sup>6</sup> Institute of Medicine. 1996. *Veterans and Agent Orange: Update*. Washington, DC: National Academy of Sciences Press.
- <sup>7</sup> Institute of Medicine. 1998. *Veterans and Agent Orange: Update*. Washington, DC: National Academy of Sciences Press.
- <sup>8</sup> Institute of Medicine. 2001. *Veterans and Agent Orange: Update 2000*. Washington, DC: National Academy Press.
- <sup>9</sup> Giri VN, Cassidy AE, Beebe-Dimmer J, Smith DC, Bock CH, Cooney KA. Association between Agent Orange and prostate cancer: a pilot case-control study. *Urology*. 2004 Apr;63(4):757-60; discussion 760-1.
- <sup>10</sup> Stellman JM, Stellman SD, Weber T, Tomasallo C, Stellman AB, Christian R, Jr. A geographic information system for characterizing exposure to Agent Orange and other herbicides in Vietnam. *Environ Health Perspect* 2003;111:321-328.
- <sup>11</sup> Stellman SD, Stellman JM. Exposure opportunity models for Agent Orange, dioxin, and other military herbicides used in Vietnam, 1961-1971. *J Expos Analysis Environ Epidemiol* (in press).
- <sup>12</sup> Bilgrad R (2000). *National Death Index User's Manual*. Hyattsville, MD: National Center for Health Statistics (reprinted January, 2003).